Regarding the Am ndments
The foregoing claim amendments are being made to expedite prosecution, but are made without prejudice to the potential pursuit of claims of the same or similar scope in this or related cases.

Remarks

Restriction/Election. In order that this constitute a complete response, Applicants affirm their election of Group I, but do so with traverse. Applicants request that the restriction requirement be reconsidered, revised and/or clarified based on the following remarks.

First, since Group 1 is drawn to compounds of claims 1 and 20, and since those claims are generic to the subject matter of their dependent claims 9-19 and 21 – 39, it would be logical, proper and efficient, if not necessary, to examine those dependent claims at the same time. Thus, we assume that Group I should include at least claims 1 – 39. Clarification would be appreciated that this is what was intended.

Secondly, claims 42-44 embrace the epimerization of aldols generically, extending beyond the production of the specific compounds of claims 1 – 40. If this case has to be restricted, we propose putting claims 42 – 44 into Group III and moving claim 77 along side claim 45 in Group I. This would be consistent with the view that compounds, their compositions, their methods of use and process of making them are a single inventive concept. Later, upon a finding of patentable subject matter, we request reconsideration of the restriction and potential consideration of claims 42 – 44 as well, given their relationship to claims 45 and 77.

Thirdly, upon a finding of patentable subject matter in the examination of Group I, we request reconsideration and rejoinder of the Group II claims which cover use of the claimed compounds in multimerizing proteins.

Abstract. A replacement abstract is attached that is believed to be responsive to the Examiner's suggestions.

Rejection under 35 USC §112, 2d Paragraph

Claim amendments have rendered moot a number of the §112, 2d paragraph issues raised in the Office Action. Other such issues are addressed below.

(1) Claims were rejected based on an alleged lack of definiteness in the definitions of R^{28} and R^{43} resulting from use of the terms "aliphatic" and "acyl". The Office Action indicated that it is unclear what the aliphatic or acyl moiety may or may not be.

This ground for rejection is traversed. The claim covers compounds containing <u>any</u> aliphatic or acyl moiety at the relevant position. That meaning, while generic, is manifest—not unclear. The term "aliphatic" is defined in the specification on page 30, line 34 – page 35,

line 13, with reference to additional defined terms (see e.g., page 31, lines 15 et seq.).

> The term "aliphatic" as used herein includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. Unless otherwise specified, alkyl, other aliphatic, alkoxy and acyl groups preferably contain 1-8, and in many cases 1-6, contiguous aliphatic carbon atoms. Illustrative aliphatic groups thus include, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH2 cyclopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH2-cyclobutyl, n-pentyl, sec pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH2-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl, -CH2 cyclohexyl moieties and the like, which again, may bear one or more substituents.
>
> Examples of substituents include: -OH, -OR2', -SH, -SR2',-CHO, =O, -COOH (or ester, carbamate, urea, oxime or carbonate thereof), -NH2 (or substituted amine, amide, urea, carbamate or guanidino derivative therof), halo, trihaloalkyl, cyano, -SO2-CF3, -OSO2F, -OS(O)2R11, -SO2-NHR11, -NHSO2-R11, sulfate, sulfonate, aryl and heteroaryl moieties. Aryl and heteroaryl substituents may themselves be substituted or unsubstituted (*e.g.* mono-, di- and tri-alkoxyphenyl; methylenedioxyphenyl or ethylenedioxyphenyl; halophenyl; or -phenyl-C(Me)2-CH2-O-CO-[C3-C6] alkyl or alkylamino).
>
> The term "aliphatic" is thus intended to include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties.

The term "acyl" is an art-recognized term that is commonly found in US patent claims, indicating its legal acceptability. The following recent patents illustrate the use of the term in claims, typically without any further limitation or description:

US Patent No. 6,291,452 1,4-benzodiazepinones and their uses as CCK antagonists
US Patent No. 6,277,984 Monomethine cyanines rigidized by a two-carbon chain
US Patent No. 6,271,371 Oxidative process and products thereof
US Patent No. 6,271,251 Substituted guanidine derivatives, process for production thereof, ...
US Patent No. 6,187,774 Fused heterocyclic compounds and pharmaceutical applications thereof
US Patent No. 6,177,439 Water soluble analogues of 20(S)-camptothecin

(2) Claims were rejected based on an alleged lack of definiteness in the definitions of R^A and R^B resulting from use of the terms "heteroaliphatic", "aryl" and "heteroaryl" which was said to be unclear.

This ground for rejection is traversed. Each of the cited terms is carefully defined and exemplified in the specification, see e.g. page 32, 1st paragraph ("heteroaliphatic"),

> The term "heteroaliphatic" as used herein refers to aliphatic moieties which contain one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched or cyclic and include heterocycles such as morpholino, pyrrolidinyl, *etc.*

and 3d paragraph ("aryl" and "heteroaryl"):

The terms "aryl" and "heteroaryl" as used herein refer to stable mono- or polycyclic, heterocyclic, and polyheterocyclic unsaturated moieties having 3 - 14 carbon atoms which may be substituted or unsubstituted. Substituents include any of the previously mentioned substituents. Non-limiting examples of useful aryl ring groups include phenyl, halophenyl, alkoxyphenyl, dialkoxyphenyl, trialkoxyphenyl, alkylenedioxyphenyl, naphthyl, phenanthryl, anthryl, phenanthro and the like. Examples of typical heteroaryl rings include 5-membered monocyclic ring groups such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl and the like; 6 membered monocyclic groups such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like; and polycyclic heterocyclic ring groups such as benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, benzothiazole, benzimidazole, tetrahydroquinoline cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, phenoxazinyl, and the like (see *e.g.* Katritzky, Handbook of Heterocyclic Chemistry). The aryl or heteroaryl moieties may be substituted with one to five members selected from the group consisting of hydroxy, C1-C8 alkoxy, C1-C8 branched or straight-chain alkyl, acyloxy, carbamoyl, amino, N-acylamino, nitro, halo, trihalomethyl, cyano, and carboxyl. Aryl moieties thus include, *e.g.* phenyl; substituted phenyl bearing one or more substituents selected from groups including: halo such as chloro or fluoro, hydroxy, C1-C6 alkyl, acyl, acyloxy, C1-C6 alkoxy (such as methoxy or ethoxy, including among others dialkoxyphenyl moieties such as 2,3-, 2,4-, 2,5-, 3,4- or 3,5-dimethoxy or diethoxy phenyl or such as methylenedioxyphenyl, or 3-methoxy-5-ethoxyphenyl; or trisubstituted phenyl, such as trialkoxy (*e.g.*, 3,4,5-trimethoxy or ethoxyphenyl), 3,5-dimethoxy-4-chloro-phenyl, *etc.*), amino, SO2NH2, -SO2NH(aliphatic), -SO2N(aliphatic)2, -O-aliphatic-COOH, and -O-aliphatic-NH2 (which may contain one or two N-aliphatic or N-acyl substituents).

We note here too that "aryl" and "heteroaryl", without further limitation, are commonly used in claims in issued US patents, reflecting their clear meaning in the art and their acceptability in patent claims.

(3) The phrase "pharmaceutically acceptable derivative" was cited as indefinite on the grounds that its metes and bounds are not known.

This ground for rejection is traversed. The Examiner's attention is respectfully directed to page 30, lines 23 – 33 of the specification for a detailed definition of "pharmaceutically acceptable derivatives", as that phrase is used in the patent application:

Also included are pharmaceutically acceptable derivatives of the foregoing compounds, where the phrase "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, carbamate, or salt of such ester or carbamate, of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a 28-epirapalog as described herein, or a metabolite or residue thereof. Pharmaceutically acceptable derivatives thus include among others pro-drugs of the rapalogs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety which is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester which is cleaved *in vivo* to yield a compound of interest. Various pro-drugs of rapamycin and of other compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention.

The Examiner's suggestion for more proper Markush language is gratefully acknowledged and reflected in the claim amendments.

(4) While the claimed compounds have a defined stereochemistry at position C28, as well as at other positions where a fixed orientation is indicated in the various structures (unless otherwise indicated), stereoisomerism can occur elsewhere, e.g. in the case of a chiral "R" group. The reference to pure stereoisomer or mixture of stereoisomers refers to stereoisomerism at such positions where a specific stereochemical orientation is not depicted. This would be clear to the ordinarily skilled artisan reading the document. However, in the interest of advancing prosecution, the phrase has been deleted. The change is not intended to affect the scope of the claims since compounds of the depicted structures would be covered by the claims regardless of their degree of isomeric purity.

(5) Claim 42 already contains all of the limitations intended by applicants in claiming their method. The claimed method is broadly useful for epimerizing aldols, generally, and is drafted accordingly.

Rejection under 35 USC §103

Grinfield et al WO 98/09972) discloses some rapamycin derivatives with unnatural stereochemistry—but does *not* disclose compounds defined by applicants' pending claims. It does not disclose or suggest epimerization of the hydroxyl at position 28 except in combination with specific other changes in the cyclohexyl moiety. Nor does it disclose or suggest epimerization at position 28 in combination with modification at positions 24 and/or 30 as embodied by the compounds of applicants' claim 20 and claims dependent thereon.

Significantly, this failure to suggest applicants' combinations of modifications (or lack thereof) must be viewed against a background knowledge of the possibility of a variety of possible modifications to the rapamycin molecule, including at positions 13, 14 and 30 (using applicants' numbering). It is important to appreciate that it was in clear view of that knowledge (see Grinfield, page 2, lines 20 – 30) that Grinfield neither suggests the possibility of producing applicants' claimed compounds nor the desirability of trying to produce such compounds.

While it is often true that a skilled chemist would in some cases expect structurally similar molecules to have functionally similar properties, that is not necessarily the case here. In fact, it was already known that seemingly small structural modifications to rapamycin resulted in significant changes in biological activity. See e.g. Luengo et al, Chemistry and Biology, July 1995 2:471-481. Consider also applicants' comparative data on page 76 of their specification. In experiments reported in Example 2.5, applicants found that epimerization of the C-28 hydroxyl group led to a *10-fold* reduction in activity in the splenocyte assay relative to rapamycin—but without loss of activity in applicants' transcription system.

So, in view of Grinfield's failure to disclose or suggest applicants' invention, reconsideration and withdrawal of the §103 rejection is requested.

Conclusion

The claims are believed to be free of the art, clear in meaning and well supported by the specification. Their allowance is earnestly requested. If a telephone discussion with applicants' attorney might be of any assistance in advancing prosecution of this case, the Examiner is invited to call him at the number provided below.

Respectfully submitted,

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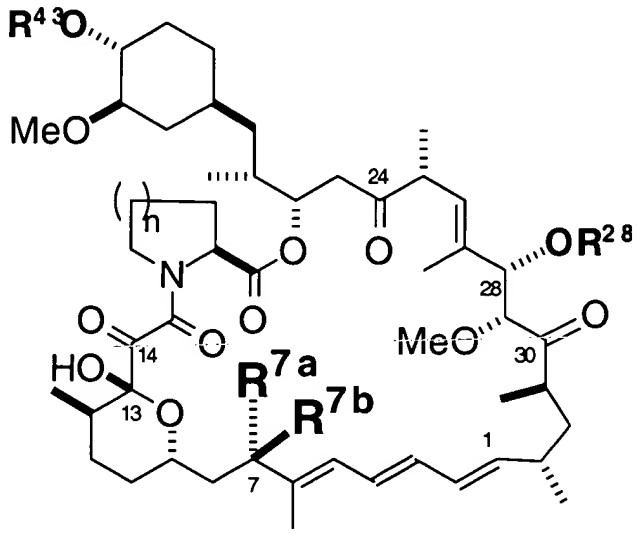
I hereby certify that this paper is being deposited on **November 13, 2001** with the United States Postal Service, as First Class Mail with sufficient postage, and is addressed to Assistant Commissioner for Patents, Washington, DC 20231 pursuant to 37 CFR 1.10

Signed Sue Watson Date 11-13-01

Clean Copy of Amended Claims 1 and 20

1 (amended). A compound of the formula:

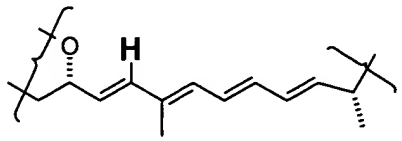


wherein

n is 1 or 2;

R^{28} and R^{43} are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

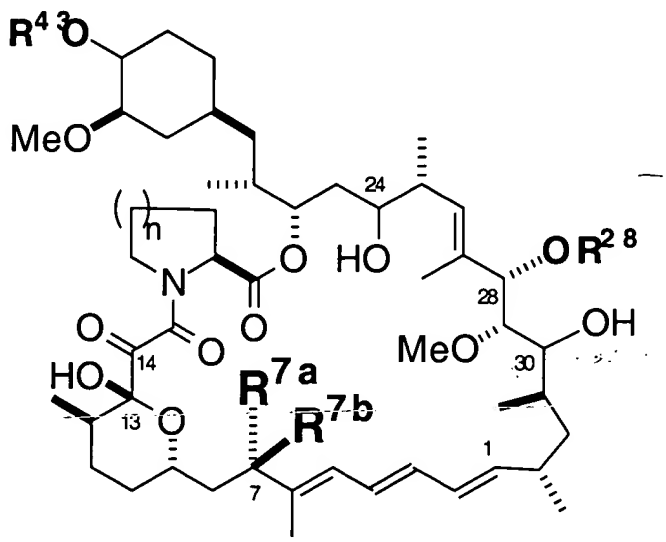
one of R^{7a} and R^{7b} is H and the other is halo, $-R^A$, $-OR^A$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO_2R^A$ or $-NR^BSO_2NR^AR^{B'}$; or R^{7a} and R^{7b}, taken



together, are H in the tetraene moiety:

where R^A is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety and where R^B is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety; or a pharmaceutically acceptable derivative thereof.

20 (amended). A compound of the formula:

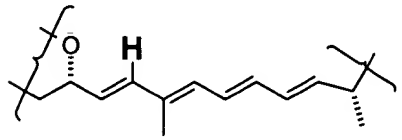


wherein

n is 1 or 2;

$\mathbf{R^{28}}$ and $\mathbf{R^{43}}$ are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

one of $\mathbf{R^{7a}}$ and $\mathbf{R^{7b}}$ is H and the other is halo, $-\mathbf{R^A}$, $-O\mathbf{R^A}$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO_2R^A$ or $-NR^BSO_2NR^AR^{B'}$; or $\mathbf{R^{7a}}$ and $\mathbf{R^{7b}}$, taken



together, are H in the tetraene moiety:

where $\mathbf{R^A}$ is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety and where $\mathbf{R^B}$ is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety; or a pharmaceutically acceptable derivative thereof.

28-EpiRapalogs

Abstract

Rapamycin derivatives containing substituents at C-28 in the epi orientation relative to rapamycin are disclosed, together with methods for their preparation and use, e.g. for regulation of biological phenomena in engineered cells. The compounds may contain optional additional modifications relative to rapamycin, as disclosed herein.